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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,473	07/30/2002	Ronald de Groot	294-120 PCT/US	4102

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,473	DE GROOT ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39,41-44 and 46-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,41-44 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/04 has been entered.

Claims 39, 41-44 and 46-48 are currently pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 39, 41-44 and 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39, 44, 47 and 48 are vague and indefinite because they recite "or a homologous protein thereof, wherein the protein or homologous protein has opsonophagocytic activity...". The specification teaches that the protein having SEQ ID NO:2 is a protease activator protein. The protein does not have opsonophagocytic activity. The specification teaches that hyperimmune sera raised against the isolated protein having SEQ ID NO:2 has opsonophagocytic activity, but the protein of SEQ ID NO:2 does not have this activity. Accordingly, the claim is vague and confusing. It is

unclear what is meant by the claim. Additionally, the structure of the 'homologous protein thereof' is not understood. The claims, nor the specification, provide a clear definition as to how the structure of the "homologous" protein is different. The terms "homologous" they are accompanied by a precise and exact definition as to how the protein structure differs. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. Additionally, no proteins have been taught to have opsonophagocytic activity, only hyperimmune sera. This renders the claim even more unclear. See also 112, first enablement rejection below.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39, 41-44 and 46-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "an immunogenic composition comprising an isolated protease maturation protein of *S.pneumoniae*, wherein the protein has an amino acid sequence as set forth in SEQ ID NO:2" and methods of raising an immune response against *S.pneumoniae* through the administration of said compound, methods of preparing these proteins and carriers comprising these proteins, does not reasonably provide enablement for "an immunogenic composition comprising

an isolated protease maturation protein of *S.pneumoniae*, wherein the protein has an amino acid sequence as set forth in SEQ ID NO:2, and/or *a homologous protein thereof*, wherein *the protein or homologous protein has opsonophagocytic activity*...", nor does it enable methods of raising an immune response to a streptococcal infection using said *homologous* protein or a protein having SEQ ID NO:2 which has *opsonophagocytic activity.* Methods of preparing these proteins or carriers comprising these proteins are also not enabled. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the instant claims contain proteins and amino acid sequences other than what is specified in the sequence disclosure, e.g., homologous proteins having opsonophagocytic activity. The specification provides a general statement that homologous or functionally homologous sequences are included; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein s sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial

orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The instant claims are drawn to proteins which are homologous or vary from a given protein; i.e., equivalent sequences, homologous sequences, fragments, etc.. The position and individual amino acid residues in peptide antigen-antibody interactions is extremely important. Selective point mutation to one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native protein on the *S.pneumoniae* bacteria, and be ineffective in treating infections caused by *S.pneumoniae*. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a dingle amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by,

and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study.

The specification and claims recite homologous and/or functionally homologous proteins to SEQ ID NO:2 yet provide no teaching or guidance as to the structure of these proteins or how to isolate/make them. It is unclear which portions of the sequence are required to retain function.

Additionally, the claims read on homologous proteins from any species of bacteria, yet the specification has only taught and exemplified the protease maturation protein having SEQ ID NO:2 from *S.pneumoniae*. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

The specification provides teaches how to make hyperimmune serum through injection of the full-length protein set forth in SEQ ID NO:2. In vitro assays that

demonstrate the ***serum's*** opsonophagocytic activity are provided. However, it is not taught that the protein or a homologous protein as required by the claims has this opsonophagocytic activity. Only the immune serum raised against the protein has opsonophagocytic activity. Accordingly, the instant claims are not enabled.

The enablement and written description in this case only sets forth SEQ ID NO:2. With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed homologous or functionally homologous proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate enablement and written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. Without specific guidance from the specification, it would take undue experimentation for those skilled in the art to make and/or use the claimed homologous and functionally homologous proteins. As stated in the 112 second paragraph rejection above, it is unclear what structures are considered to represent a homologous or functionally homologous protein. Without specific guidance from the specification, it would take undue experimentation for those skilled in the art to make and/or use the claimed invention.

Response to Applicants' arguments to 112, 1st and 2nd paragraph rejections:

Applicants have argued that the specification provides a clear definition of the term "homologous". They state that proteins with an E-value (except value) of more than 10^{-10}, as determined by Blast or Blastp computer programs are not considered to

be homologous. See page 4 of Applicant's response filed on 3/31/05. This has been fully and carefully considered but is not deemed persuasive in overcoming the rejections. Applicants argument is not commensurate in scope with the claimed invention. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. Additionally, no proteins have been taught to have opsonophagocytic activity, only hyperimmune sera. Additionally, the formulas plugged into the Blast/Blastp computer program can be manipulated thereby changing what would constitute a protein which is not more than 10^{-10}. Additionally, there is no teaching that proteins that meet this criteria are opsonophagocytic, much less able to raise an immune response against *S.pneumoniae.* The term "homologous" allows for proteins from any source, even those of different Genus. The specification clearly has not taught any other proteins other than the one possessing the amino acid sequence set forth in SEQ ID NO:2. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every

aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Only hyperimmune sera raised against the isolated protein has been shown to have opsonophagocytic activity. The protein, itself, nor any other homologous proteins have not been shown to have this activity. They are protease maturation proteins, not opsonophagocytic.

Applicants also argue that since the protein having SEQ ID NO:2 is a conserved protein, one of skill in the art would inherently know which amino acids could be substituted or deleted. This is not deemed persuasive. it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The instant claims are drawn to proteins which are homologous or vary from a given protein; i.e., equivalent sequences, homologous sequences, fragments, etc.. The position and individual amino acid residues in peptide antigen-antibody interactions is extremely important. Selective point mutation to one key antigen residue could eliminate the ability of an antibody to recognize this altered

antigen. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native protein on the *S.pneumoniae* bacteria, and be ineffective in treating infections caused by *S.pneumoniae*. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a dingle amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study.

Claim Rejections - 35 USC § 102

5. Claims 39, 41-44 and 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunsch et al (WO 98/18930).

Kunsch et al teach antigens and vaccines to prevent or attenuate infections caused by bacteria of the *Streptococcus* genus and *S.pneumoniae* in particular. See abstract and page 115. The vaccine encompasses a polypeptide or fragment thereof

contained in Table 1. Table 1 discloses a polypeptide which has 213 identical amino acids to Applicants' SEQ ID NO:2 which is 322 amino acids in length. The instant claims encompass fragments and use the open language "comprising" . Accordingly, the polypeptide and/or its fragments to be used in the vaccines read on the instant claims. A protein with this large of a conserved region would inherently be homologous and/or functionally homologous. This protein and its fragments would be expected to raise a very similar or homologous immune response. The reference teaches that the vaccine may be prepared with a carrier and/or an adjuvant and is suitable to elicit protective antibodies in the vaccinated animal. See pages 4-5. Although the reference does not use the name "protease maturation protein" to describe their protein, the structure is the same and therefore the protein would inherently possess this function. Recombinant methods of producing the protein and/or epitope-bearing portions are also taught. See page 3, line 32- page 33, line 5. Claim 42 allows for homologous proteins to the strains Ft231 or EF3296 and therefore is anticipated by the reference. Applicants should limit their claims to the full-length sequence of SEQ ID NO:2.

Response to Applicants' arguments:

Applicants argue that Kunsch which has 213 of 322 amino acids in common with the protein set forth in SEQ ID NO:2 is not homologous because it does not have an Expect value of not more than 10^{-10}, as determined by Blast or Blastp computer programs. The Declaration of inventor, Peter Wilhelmus Maria Hermans, is cited. This argument has been fully and carefully considered but is not commensurate in scope with the claimed invention. The instant claims do not require any structure with the term

"homologous". A protein having such a high degree of similarity, such as the one taught by Kunsch, would meet the art's definition of homologous. "Homologous" can be interpreted as broadly as having just a few amino acids in common. Additionally, the specification fails to show any homologous proteins which possess opsonophagocytic activity.

6. Claims 39, 41-44 and 46-48 are rejected under 35 U.S.C. 102(e) as being anticipated by Black et al (US 6,348,328 B1).

Black et al teach a polypeptide which has 48 identical amino acids to Applicants' SEQ ID NO:2 and a 97% local similarity. Black et al teach that the polypeptide is from *S.pneumoniae.* It is taught that the proteins or their fragments may be used in pharmaceutical compositions or vaccines along with a carrier and or an adjuvant to treat infections caused by the bacteria. The manufacture of such medicaments is also taught. See columns 16-17. See column 20, lines 33-41 for vaccine teachings. Recombinant production of the polypeptides is also taught. Although the reference does not use the name "protease maturation protein" to describe their protein, the structure is the same and therefore the protein would inherently possess this function. The instant claims include "homologous" polypeptides. This large fragment taught by Black is a 'homologous' sequence. Applicants have amended the claims from the term "immunogenic fragment", but the claims still read on these fragments. The specification provides no clear description of what structures are required for a protein to be considered 'homologous'. The specification does teach that fragments of 5-8 amino acids in length and preferably 10-15 amino acids in length are included in the scope of

invention. Claim 42 allows for homologous proteins to the strains Ft231 or EF3296 and therefore is anticipated by the reference. Black's fragments anticipate the claims.

Response to Applicants' arguments:

Applicants argue that the Black protein which has 48 contiguous amino acids in common with the protein set forth in SEQ ID NO:2 is not homologous because it does not have an Expect value of not more than 10^{-10}, as determined by Blast or Blastp computer programs. The Declaration of inventor, Peter Wilhelmus Maria Hermans, is cited. This argument has been fully and carefully considered but is not commensurate in scope with the claimed invention. The instant claims do not require any structure with the term "homologous". A protein having such a high degree of similarity, such as the one taught by Kunsch, would meet the art's definition of homologous. "Homologous" can be interpreted as broadly as having just a few amino acids in common. Additionally, the specification fails to show any homologous proteins which possess opsonophagocytic activity.

7. Claims 39, 42, 43, 47 and 48 are rejected under 35 U.S.C. 102(a) as being anticipated by Swiss Prot. Accession No. Q02473, P15294 AND P14308 (April 7, 1999) in light of Applicant's admissions on page 5, lines 8-14 of the specification. These references are not included in a PTO-892 since they were cited by Applicant.

The references teach protease maturation proteins from *Lactobacillus paracasei, Lactococcus lactis subspec. lactis,* and *Lactococcus lactis subspec. cremoris,* respectively. The specification teaches that these prior art proteins are related (homologous) to the protein set forth in SEQ ID NO:2. The molecular weight of these

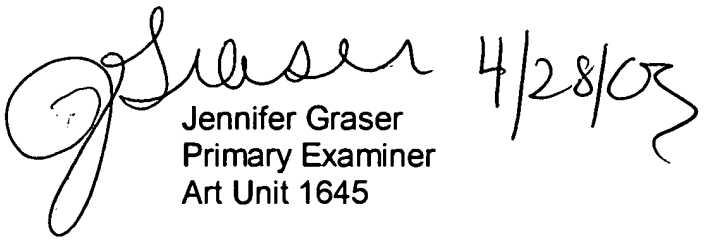
proteins also correspond to Applicants Pmp. See page 5, lines 8-14 of the instant specification. Applicants compared their protein set forth in SEQ ID NO:2 against known databases and discovered that it was homologous to these *Lactobacillus/Lactococcus* Pmp proteins. Accordingly, the references read on "proteins homologous to SEQ ID NO:2" As stated above, the claimed protein does not have opsonophagocytic activity, only its antibodies do so the references anticipate the claims. Additionally, the proteins of the prior art are similar enough to the Pmp of *S.pneumoniae* that they would inherently raise an immune response to *S.pneumoniae*. Claim 42 allows for homologous proteins to the strains Ft231 or EF3296 and therefore is anticipated by the references. In claim 48, "carrier" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.



Jennifer Graser
Primary Examiner
Art Unit 1645